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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,438	11/14/2001	Avi J. Ashkenazi	10466/201	2374

35489 7590 04/20/2004

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,438	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 November 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/28/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The preliminary amendments filed 11/14/01 and 9/03/02 have been entered.

Specification

The disclosure is objected to because of the following informalities:. on p. 548, line 19, "samples" should be "sample".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 119-124, 127, 128, and dependent claims 125, 126 and 129-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 119-124, 127, 128 are indefinite for reciting "extracellular domain". The protein identified as PRO290 is disclosed as an intracellular protein (p. 340, line 20). It is not disclosed as being expressed on a cell surface. Accordingly, the limitation that the claimed protein comprises an "extracellular domain" (for example see claim 119, parts (c) and (d)) is indefinite, as the art does not recognize intracellular proteins as having such a domain. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain..."lacking its associated signal sequence" (claim 39, part (d), for example) is indefinite because a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 119-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to a polypeptide. While the disclosed nucleic acid of SEQ ID NO:33, which encodes the protein called PRO290, has utility as a screening probe to detect squama cell-type lung carcinomas (pages 550, TABLE 9A), the polypeptide has not such utility. There is no specific or substantial function attributable to the polypeptide, and even though it is stated that PRO290 is most related to FAN and beige proteins (p. 410, line 18), a shared identity of less than 20% is too low to reliably extrapolate function from structure (see SEQUENCE COMPARISON US 5,952,223). Further, the function of these proteins was unclear in the prior art. The prior art does not provide sufficient information to allow the skilled artisan to use PRO290 without significant further research.

Even though the nucleic acid has utility as a probe for screening for lung tumor cells, the encoded polypeptide has no such utility since there is no reason to suspect that there is alteration of polypeptide sequence or amount in lung tumor *versus* normal tissue. Even if the DNA has utility as a lung tumor marker, the encoded protein does not have utility because it is not known what the protein does or if the level of PRO290 protein in lung tumors corresponds to nucleic acid transcript level, *i.e.*, if an increased gene amplification in lung tumors corresponds to an increased amount of expressed protein. It does not necessary follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development. For example, Pennica et al. (1998, PNAS USA 95, p.14722, second paragraph) teach that:

> An analysis of WISP-1 gene amplification and expression in human coon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient.

Additionally, Hayes et al. (Electrophoresis 19 :1862-1871, 1998) studied 80 proteins relatively homogenous in half-life and expression level, and found no strong correlation between protein and transcript levels; for some genes, equivalent mRNA levels translated into protein abundances which varied by more than 50-fold. It was concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and

Figure 1). Therefore, because it cannot be concluded that PRO290 is associated with formation or growth of lung tumor or is useful itself as a diagnostic marker for lung cancer, the encoded protein does not have utility. Significant further research would be required to find out what the protein does and if and how it is linked to lung cancer.

For these reasons, there is no substantial and specific utility for the claimed polypeptide.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

The specification provides little beyond structural data and potential activities of the PRO290 polypeptide without guidance about which specific activities one could reasonably expect the polypeptide to possess as discussed above. Also, the claims have great breadth allowing for 80% identity to a partial sequence. Therefore, it would require undue experimentation to use the claimed invention. For these reasons which include breadth of the claims, lack of information on the relationship of structure to function of PRO290, paucity of information in the prior art, limited working example, and lack of guidance for use provided in the specification, it would require undue experimentation to use the claimed nucleic acid commensurate in scope with the claims.

Claims 119-124, 126, 128 and 132-138 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims lack written description on two counts. First, claims are drawn to, for example, a polypeptide of SEQ ID NO:33 lacking its associated signal sequence. It is not clear if PRO290 has a signal sequence or if it does, what that sequence is. The specification discloses PRO290 of SEQ ID NO:33, but no domains are disclosed. The specification says PRO290 is believed to be an intracellular protein (p. 349, line 20). While there is some relationship to intracellular proteins FAN and beige (p. 410, line 18), shared sequence identity is not high (less than 20%, see SEQUENCE COMPARISON US 5,952,223) so correspondence to structure is difficult to make. It does not appear Applicants were in possession of a polypeptide specifically lacking (or specifically including) a signal sequence.

Second, the claims are drawn to polypeptides having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Which polypeptides of the genus comprising the required sequence are part of the invention has not been set forth.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only a polypeptide of SEQ ID NO:33, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

Priority

Priority application 09/380,137 and earlier filed priority applications do *not* meet the requirements of 35 U.S.C. § 112, first paragraph. While the sequence of PRO290 is disclosed, there was no function/use known to be associated with PRO290, and the skilled artisan would not have known how to use it. Therefore, the prior application also does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 120. Note that even if priority were granted to the earliest filed priority application 60/092,472, the art rejection would remain under 35 UCS 102(a).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 119-123, 126, 128 are rejected under 35 U.S.C. 102(b) as being anticipated by GenBank AB011112.1.

GenBank AB011112.1 teaches a nucleic acid encoding a protein at least 99% identical to SEQ ID NO:33 of the instant application. See attached SEQUENCE COMPARISON GenBank AB011112.1.

Conclusion

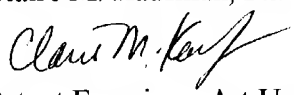
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571)272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571)272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

April 15, 2004

SEQUENCE COMPARISON GenBank AB011112 Part of 09/990,438 page 8

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AC   O60288;
DT   01-AUG-1998 (TrEMBLrel. 07, Created)
DT   01-OCT-2002 (TrEMBLrel. 22, Last sequence update)
DT   01-MAR-2003 (TrEMBLrel. 23, Last annotation update)
DE   KIAA0540 protein (Fragment).
GN   KIAA0540.
OS   Homo sapiens (Human).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
OX   NCBI_TaxID=9606;
RN   [1]
RP   SEQUENCE FROM N.A.
RC   TISSUE=Brain;
RX   MEDLINE=98290545; PubMed=9628581;
RA   Nagase T., Ishikawa K., Miyajima N., Tanaka A., Kotani H., Nomura N.,
RA   Ohara O.;
RT   "Prediction of the coding sequences of unidentified human genes. IX.
RT   The complete sequences of 100 new cDNA clones from brain which can
RT   code for large proteins in vitro.";
RL   DNA Res. 5:31-39(1998).
DR   EMBL; AB011112; BAA25466.3; -  .
DR   InterPro; IPR000409; Beige_BEACH.
DR   InterPro; IPR001680; WD40.
DR   Pfam; PF02138; Beach; 1.
DR   Pfam; PF00400; WD40; 2.
DR   ProDom; PD007848; Beige_BEACH; 1.
DR   SMART; SM00320; WD40; 3.
DR   PROSITE; PS50197; BEACH; 1.
DR   PROSITE; PS50082; WD_REPEATS_2; 2.
DR   PROSITE; PS50294; WD_REPEATS_REGION; 1.
KW   Repeat; WD repeat.
FT   NON_TER       1      1
SQ   SEQUENCE   2041 AA;  224474 MW;  CC523F1D5D041F51 C   RC64;

  Query Match             99.5%;  Score 5222;  DB 4;  Length 2041;
  Best Local Similarity   97.1%;  Pred. No. 0;
  Matches 1003;  Conservative    0;  Mismatches    0;  Indels   30;  Gaps    1;

Qy          1 MSQFEMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSRRAFQELVLEPAQRRARLE 60
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Db       1009 MSQFEMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSRRAFQELVLEPAQRRARLE 1068

Qy         61 GLRYTAVLKQQATQHSMALLHWGALWRQLASPCGAWALRDTPIPRWKLSSAETYSRMRLK 120
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Db       1069 GLRYTAVLKQQATQHSMALLHWGALWRQLASPCGAWALRDTPIPRWKLSSAETYSRMRLK 1128

Qy        121 LVPNHHFDPHLEASALRDNLGEVPLTPTEEASLPLAVTKEAKVSTPPELLQEDQLGEDEL 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1129 LVPNHHFDPHLEASALRDNLGEVPLTPTEEASLPLAVTKEAKVSTPPELLQEDQLGEDEL 1188

Qy        181 AELETPMEAAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFYDGSTERVETEEG 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1189 AELETPMEAAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFYDGSTERVETEEG 1248
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Qy        241 IGYDFRRPLAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKVGTTPVSSPSQTPRPQ 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1249 IGYDFRRPLAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKVGTTPVSSPSQTPRPQ 1308

Qy        301 PGPIPPHTQVRNQVYSWLLRLRPPSQGYLSSRSPQEMLRASGLTQKWVQREISNFEYLMQ 360
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Qy        361 LNTIAGRTYNDLSQYPVFPWVLQDYVSPTLDLSNPAVFRDLSKPIGVVNPKHAQLVREKY 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1369 LNTIAGRTYNDLSQYPVFPWVLQDYVSPTLDLSNPAVFRDLSKPIGVVNPKHAQLVREKY 1428

Qy        421 ESFEDPAGTIDKFHYGTHYSNAAGVMHYLIRVEPFTSLHVQLQSGRFDCSDRQFHSVAAA 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1429 ESFEDPAGTIDKFHYGTHYSNAAGVMHYLIRVEPFTSLHVQLQSGRFDCSDRQFHSVAAA 1488

Qy        481 WQARLESPADVKELIPEFFYFPDFLENQNGFDLGCLQLTNEKVGDVVLPPWASSPEDFIQ 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1489 WQARLESPADVKELIPEFFYFPDFLENQNGFDLGCLQLTNEKVGDVVLPPWASSPEDFIQ 1548

Qy        541 QHRQALESEYVSAHLHEWIDLIFGYKQRGPAAEEALNVFYYCTYEGAVDLDHVTDERERK 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        601 ALEGIISNFGQTPCQLLKEPHPTRLSAEEAAHRLARLDTNSPSIFQHLDELKAFFAE--- 657
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        658 ---------------------------VTVSASGLLGTHSWLPYDRNISNYFSFSKDPTM 690
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Qy        751 LDVVTCLALDTCGIYLISGSRDTTCMVWRLLHQGGLSVGLAPKPVQVLYGHGAAVSCVAI 810
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Db       1789 LDVVTCLALDTCGIYLISGSRDTTCMVWRLLHQGGLSVGLAPKPVQVLYGHGAAVSCVAI 1848

Qy        811 STELDMAVSGSEDGTVIIHTVRRGQFVAALRPLGATFPGPIFHLALGSEGQIVVQSSAWE 870
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Qy        871 RPGAQVTYSLHLYSVNGKLRASLPLAEQPTALTVTEDFVLLGTAQCALHILQLNTLLPAA 930
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Qy        931 PPLPMKVAIRSVAVTKERSHVLVGLEDGKLIVVVAGQPSEVRSSQFARKLWRSSRRISQV 990
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Qy        991 SSGETEYNPTEAR 1003
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Db       2029 SSGETEYNPTEAR 2041
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; Patent No. 5952223
;  GENERAL INFORMATION:
;    APPLICANT:  Kaplan, Jerry
;    APPLICANT:  Perou, Charles
;    APPLICANT:  Moore, Karen
;    TITLE OF INVENTION:  COMPOSITIONS FOR THE DIAGNOSIS
;    TITLE OF INVENTION:  AND TREATMENT OF CHEDIAK-HIGASHI SYNDROME
;    NUMBER OF SEQUENCES:  32
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/822,445
;      FILING DATE:  21-MAR-1997
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  2186 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  unknown
;    MOLECULE TYPE:  protein
;    FRAGMENT TYPE:  internal
US-08-822-445-2

  Query Match             16.8%;  Score 882;  DB 2;  Length 2186;
  Best Local Similarity   27.9%;  Pred. No. 1.2e-70;
  Matches  295;  Conservative  147;  Mismatches  338;  Indels  276;  Gaps   43;

Qy          5 EMDTYAKSHDLMSGFWNACYDMLMSSGQRRQWERAQSR-RAFQELVLEPAQRRARLEGLR 63
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Qy         64 YTAVLKQQATQHSM---ALLHWGALWRQLASPCGAWALRDTPI---PRWKLSSAETYSRM 117
               |::     : :   |  ||    :||       |     ||     |:|   |  :|
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Qy        118 RLKL------VPNHHFDPHLEASALRD-NLGEVPLTPTEEASLPLAVTKEAKVSTPPELL 170
              | :|      :|| :         |||    |  | |      ||:   | |  :
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Qy        171 QEDQLGEDELAELETPMEAAELDEQREKLVLSAECQLVTVVAVVPGLLEVTTQNVYFY-D 229
              :|:   : :      :  |   |   :|:|  :|                    :||  |
Db       1390 VKDKAASESIRVNRRCISVAPSRETAGELLL-GKC----------------GMYFVED 1430

Qy        230 GSTERVETEEGIG----YDFRRPLAQLREVHLRRFNLRRSALELFFIDQANYFLNFPCKV 285
              ::: ||:    |      |     :::||| | : || :|:|:|  :     | |
Db       1431 NASDAVESSSLQGELEPASFSWTYEEIKEVHRRWWQLRDNAVEIFLTNGRTLLLAF---- 1486

Qy        286 GTTPVSSPSQTPRPQPGPIPPHTQVRNQVYSWLLRLRPPSQGYLSSRSPQ--EMLRASGL 343
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Db       1487 ------------------DNNKVRDDVY----------QSILTNNLPNLLEYGNITAL 1516

Qy        344 TQKWVQREISNFEYLMQLNTIAGRTYNDLSQYPVFPWVLQDYVSPTLDLSNPAVFRDLSK 403
              |  |   :|:|||||  ||  |||::||| ||||||:|  |||| ||||::|:::|:|||
Db       1517 TNLWYSGQITNFEYLTHLNKHAGRSFNDLMQYPVFPFILSDYVSETLDLNDPSIYRNLSK 1576

Qy        404 PIGVVNPKHAQLVREKYESFE----------DPAGTIDKFHYGTHYSNAAGVMHYLIRVE 453
              || |   :      : |:  |          ||   :  :|||:||||:  |:|:|:|:|:
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Qy        454 PFTSLHVQLQSGRFDCSDRQFHSVAAAWQ-ARLESPADVKELIPEFFYFPDFLENQNGFD 512
              ||| : :  |   ||  || |||    |: :  ||  ||||||||||| |:|| |: |||
Db       1637 PFTKMFLAYQDQSFDIPDRTFHSTNTTWRLSSFESMTDVKELIPEFFYLPEFLVNREGFD 1696

Qy        513 LGCLQLTNEKVGDVVLPPWA-SSPEDFIQQHRQALESEYVSAHLHEWIDLIFGYKQRGPA 571
               |  |   |:|  | ||||| : |  ||  |||||||::|| ::  ||||:|||||:| |
Db       1697 FGVRQ-NGERVNHVNLPPWARNDPRLFILIHRQALESDHVSQNICHWIDLVFGYKQKGKA 1755

Qy        572 AEEALNVFYYCTYEGAVDLDHVTDERERKALEGIISNFGQTPCQLLKEPHPTRLSAE--- 628
              : :|:|||:  || | :|:  | |  :|:||| :|  :|||| ||    | :|  |:
Db       1756 SVQAINVFHPATYFG-MDVSAVEDPVQRRALETMIKTYGQTPRQLFHTAHASRPGAKLNI 1814

Qy        629 ----------EAAHRLAR---LDTNSPSIFQHLDELKAFFAEVTVSASG--------- 664
                       : | |  |    :   ||    :  ||  : |   | |
Db       1815 EGELPAAVGLLVQFAFRETREPVKEVTHPSPLSWIKGLK--WGEYVGSPSAPVPVVCFSQ 1872

Qy        665 ------------------------LLGTH--------------------SWLPYDRNIS 679
                                     || |:                    ||  |  ||
Db       1873 PHGERFGSLQALPTRAICGLSRNFCLLMTYNKEQGVRSMNNTNIQWSAILSW-GYADNIL 1931

Qy        680 NYFSFSKDPTMG---SHKTQRLLSGPWVPGSGVSGQALAVAPDGKLLFSGGH------WD 730
                |   :| :    | :  :: |  ||            ||   ||:|        :
Db       1932 RLKSKQSEPPINFIQSSQQHQVTSCAWV-------------PDSCQLFTGSKCGVITAYT 1978

Qy        731 GSLRVTALPRGKLLSQLSC--HLDVVTCLALDTCGIY--LISGSRDTTCMVW---RLLHQ 783
              |  :     :: ||:    | : :| | :  |  |  :|| ||| ||:||   || :
Db       1979 NRLTSSTPSEIEMESQMHLYGHTEEITGLCV--CKPYSVMISVSRDGTCIVWDLNRLCY- 2035

Qy        784 GGLSVGLAPKPVQVLYGHGAAVSCVA-------ISTELDMAVSGSE------DGTVIIHT 830
                     || | || : |: |:       |:|  | |  ||:      :| :: |
Db       2036 -----------VQSLAGHKSPVTAVSASETSGDIATVCDSAGGGSDLRLWTVNGDLVGH- 2083

Qy        831 VRRGQFVAAL----RPLGATFPGPIFHLALGSEGQIVVQSSAWE-------------RPG 873
              |   : : ::    :| | :    |  :| | |  ||   | |:             :|
Db       2084 VHCREIICSVAFSNQPEGVS----INVIAGGLENGIVRLWSTWDLKPVREITFPKSNKPI 2139

Qy        874 AQVTYSL---HLYSVNG----------KLRASLPL 895
              :|:|    |||: |           : |  ||:
Db       2140 ISLTFSCDGHHLYTANSEGTVIAWCRKDQQRVKLPM 2175
```